Witnessing a New Era? – The Emerging Role of Targeted Drugs in the Medical Treatment of Advanced Medullary and Anaplastic Thyroid Cancer

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Abstract

The treatment of advanced thyroid cancer is currently entering a new era due to the introduction of targeted therapy into modern cancer treatment. The growing insight into the molecular biology of thyroid cancer and on the development of numerous mainly multitargeted agents provide the basis for new treatment strategies. In particular, activation of mitogenic and angiogenic signalling pathways are suitable targets as preclinical and clinical data suggest. Several Phase II and a few Phase III studies were launched in thyroid cancer which included medullary thyroid cancer (MTC) and anaplastic thyroid cancer (ATC) but only a few focused specifically on theses subtypes. A number of smaller Phase II trials reported promising response rates and progression-free survival. Results from a randomised Phase III trial in MTC with vandetanib, a combined vascular endothelial growth factor receptor 2 + 3 (VEGF-R2+3) and RET multi tyrosine kinase inhibitor demonstrated significant clinical activity and resulted in the first approval of a kinase inhibitor for the treatment of MTC in 2011. Unlike in MTC, in ATC the prognosis is dismal due to the aggressive nature of the disease. Some mainly vascular targeting agents alone or in combination with chemotherapy have shown interesting activity in this disease and have raised new hope. Particularly the combination of fosbretabulin with a chemotherapy backbone of paclitaxel and carboplatin tripled the one-year survival rate in a recent Phase II trial which included 80 patients with ATC. In this review, we provide a brief overview of the general treatment concept of MTC and ATC and summarise the compiled evidence published on targeted agents in these rare thyroid cancer subtypes.

Keywords

Anaplastic thyroid cancer, medullary thyroid cancer, targeted drugs, multimodality treatment

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Malignancies of the thyroid can be classified as either of follicular cell origin or parafollicular C-cell origin. The cancers of follicular origin include papillary thyroid cancer (PTC), follicular thyroid cancer (FTC) and Hurthle cell cancer commonly referred together as differentiated thyroid cancer (DTC), poorly differentiated thyroid cancer (PDTC) and anaplastic thyroid cancer (ATC).[1] Medullary thyroid cancer (MTC) originates from the parafollicular C-cells.[1] PTC and FTC account for more than 80–90 % of all thyroid cancers, MTC for about 4 %, PDTC for about 5–10 % and ATC for 2–5 %.[1,2] Although ATC represents only a minority of all thyroid cancer cases, it accounts for approximately 50 % of all thyroid cancer-related death.[3] Its highly aggressive nature is underscored by a median survival rate of less than six month following diagnosis.[3,4] While ATC has an almost uniformly fatal outcome despite aggressive therapy,[1] unselected patients suffering from MTC have an overall 10-year survival of approximately 70 % following primary successful surgery[5] (see *Figure 1*). However, until recently, only limited therapeutic options existed for patients with unresectable or metastatic MTC.[6]

Unlike in more frequent types of cancer, prospective randomised trials are difficult due to the lack of sufficient number of patients. Thus advances in the clinical care of ATC and MTC has been slow and mainly depend on retrospective data analysis or limited case series or even clinical case reports.

Surgery is considered the only curative treatment option in MTC.[6] This contrasts with ATC, where the potential and optimal sequence of surgery, radiation and chemotherapy still needs to be defined.[7,8]

Advances in the understanding of molecular pathology of thyroid cancer led to the identification of a variety of potential molecular targets[9,10] which opened the avenue for the introduction of molecular targeted therapy in to the treatment concept for thyroid cancer (see *Figure 2* and *Table 1* and *2*).[9,10] This development is highlighted by the recent approval of Vandetanib by the US Food and Drug Administration (FDA) based on data from a randomised trial.

This review summarises the current standard treatment options in MTC and ATC and provides an overview on the emerging role of targeted drugs in the medical treatment of advanced medullary and anaplastic thyroid cancer.

Medullary Thyroid Cancer

Prognosis and Standard Treatment

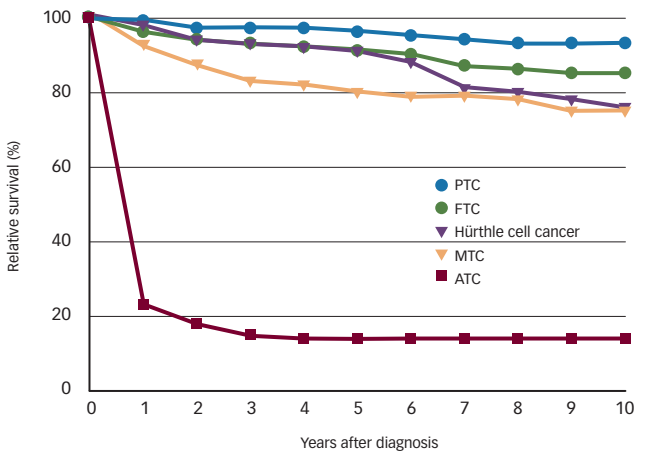
Patients age and extent of disease at the time of diagnosis are the main independent indicators for disease relapse and mortality in MTC. The preoperative level of calcitonin is capable to predict the probability for disease-free survival.[11] Post-surgery, if calcitonin is beyond the detection level after pentagastrin stimulation, patients are likely to be free of disease.[5] However, incomplete remission of calcitonin after initial surgery does not rule out long-term survival.[5] Mutation analysis of the RET proto-oncogene identified a specific activating point mutation, M918T which appears to be a strong negative prognostic indicator for progression-free survival (PFS) and OS (OS).[12] The presence of this mutation reduces the 10-year survival by half from about 90 to 45 %.[12]

Patients with RET germline mutations characteristic of the multiple endocrine neoplasia (MEN) type 2A and B syndrome are at extreme risk to develop MTC and preventive total thyroidectomy is recommended.[13] In hereditary or sporadic MTC total thyroidectomy combined with lymph node dissection of central compartments is considered the cornerstone of the primary treatment. The additional lateral lymph node dissection is usually indicated in hereditary MTC but should be performed in sporadic MTC only if lymph node metastases are suspected or dependent on the stimulated calcitonin level prior to surgery.[14,15]

Two to three months following primary resection, calcitonin drops below the detection level in 60–90 % of patients without lymph node involvement.[6] Persistence of calcitonin indicates residual disease and there seems to be a correlation between the level of calcitonin and the remaining tumour burden.[6] In the event of residual disease or disease relapse with tumour mass in the neck or mediastinum, re-operation is usually performed. However, the definitive cure rate is reported to be less than 40 % in this situation.[6] In patients with localised disease with either elevated calcitonin, microscopic residual disease or positive lymph nodes, external beam radiation was shown to reduce the risk of loco-regional tumour recurrence.[16,17] The main cause of disease-related death are distant metastases which often affect multiple organs including mainly lung, bone and liver.[6] The occurrence of distant metastases considerably affects survival rates which decline at five years to 25 % and at 10 years to 10 %, respectively.[6] In this palliative setting, the relief of symptoms and maintenance of quality of life are the major treatment goals. Calcitonin-induced diarrhoea may temporarily be controlled by either loperamide or somatostatin analogues. Beside the improvement of symptoms, somatostatin analogues alone or in combination with interferon have some efficacy to reduce serum calcitonin levels but rarely induce substantial tumour remissions.[18] Beside the application of bisphosphonates, surgery, external beam radiation or chemoembolisation may be useful to treat bone metastases.[6] In case of clinically dominant liver metastases, chemoembolisation might be effective to reduce tumour burden and provide symptomatic relief.[19]

The effect of chemotherapy on OS is unclear due to the lack of large-scale clinical trials and until recently has been considered for the palliation of symptoms in metastatic disease particularly at the time of rapid tumour progression.[5,6] Transient tumour responses in up to 20 % have been observed with doxorubicin or aclarubicin alone. Symptomatic improvement and response rates similar to doxorubicin were observed with combinations of 5-fluorouracil/dacarbacin or 5-fluorouracil/streptocotocin.[5] However, in the light of the promising data for molecular treatment approaches a critical re-appraisal of the value of conventional chemotherapy is warranted.

Figure 1: Prognosis of Thyroid Cancer – Different Thyroid Cancer Subtypes



The survival time of thyroid cancer of different histological subtypes across all stages is illustrated. ATC = anaplastic thyroid cancer; FTC = follicular thyroid cancer; MTC = medullary thyroid cancer; PTC = papillary thyroid cancer. Source: Survival data were reproduced from Hundahl et al., 1998.[70]

Anaplastic Thyroid Cancer

Prognosis and Current Treatment

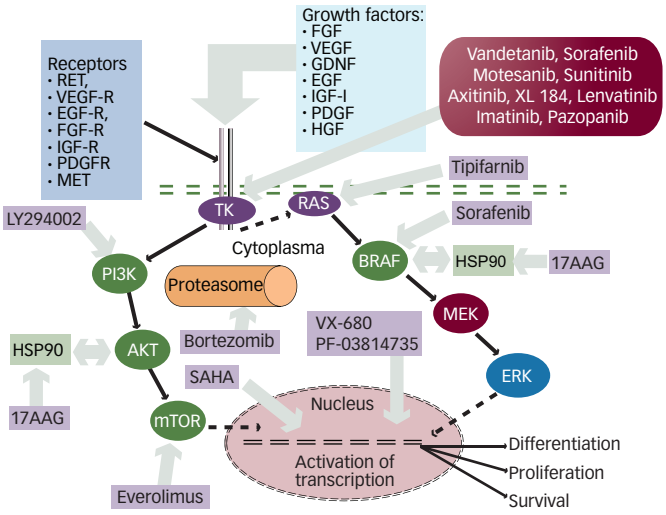
ATC usually manifests itself as a rapidly enlarging anterior neck mass with a doubling time of tumour volume sometimes of less than two weeks. This is often accompanied by dysphagia, dyspnoea or vocal cord paralysis.[20] In most of the cases, ATC is locally advanced, frequently unresectable and about 50 % of patients have metastatic disease at diagnosis.[20] Prognostic parameters are age, sex, size of the primary tumour, complete resection and extent of the disease.[21,22] Sugitani et al. defined a prognostic score which is based on the following risk factors: acute symptoms, tumour >5 cm, presence of distant metastases and white cell count >10,000 µl.[23]

As most of the patients die due to local tumour complications within a few month after diagnosis, improving the local disease control might potentially extend the OS.[8,24] While the treatment standard is still evolving, results from different retrospective studies suggested that single modality treatment is usually insufficient to achieve this goal.[21,25] Multimodality treatment of ATC typically includes surgery, radiotherapy and chemotherapy. Based on recent clinical data it appears that only a combined treatment approach may improve the clinical outcome in terms of both local and systemic disease control.[8,24]

The goal of curative surgery is to completely resect the tumour. In fact, a complete tumour resection was recently identified as a prognostic factor in clinical trials in ATC. Moreover, if potentially curative surgery is combined with post-operative adjuvant radiotherapy, this could result in a significantly increase in OS.[26,27] Given the overall still dismal prognosis, however, surgery should usually be limited to not compromise the functional anatomy of the cervical structures.

Radiation therapy could either be applied as hyperfractionated radiation alone or in combination with chemotherapy as radiosensitiser. The most commonly used drugs for radiochemotherapy are doxorubicin or mitoxantrone.[7] Radiotherapy combined with chemotherapy appeared to result in an improved OS as compared to radiotherapy alone.[28] More recent studies evaluated the curative potential of different radiation doses and data revealed that a hyperfractionated radiation regimen seems more effective than conventional treatment and that doses

Figure 2: Simplified Model of Tyrosine Kinase Receptor Pathways and Potential Targets for Molecular Targeted Therapy



The two main signalling pathways for tyrosine kinase (TK) receptors like vadcular endothelial growth factor-receptor (VEGF-R) or epidermal growth factor-receptor (EGF-R) are the Ras-Raf-mitogen-activated protein kinase (MAPK) pathway and the phosphoinositide 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR)-pathway. These pathways regulate the phosphorylation status of nuclear transcription factors and thereby regulate cellular proliferation, survival and differentiation. The figure illustrates the main drugs that act along these signal transduction pathways as well as inhibitors of aurora kinases (PF03814735, VX-680) and histone-deacetylase (SAHA). The line with a square indicates inhibition, the rhomb indicates stabilisation. FGF-R = fibroblast growth factor-receptor; GDNF = glial cell line-derived neutrophic factor; HGF = hepatocyte growth factor; HSP90 = heat shock protein 90; IGF-R = insulin-like growth factor-receptor; PDGFR = platelet-derived growth factor-receptor.

Table 1: Overview of Molecular Targets in Anaplastic and/or Medullary Thyroid Cancer

Target	Type	Reference
VEGF	ATC, MTC	1,60
Aurora B	ATC, MTC	46,71,72
IGF-IR	ATC, MTC	73,74
Ras	ATC	75
EGFR	ATC	76
MET	MTC	77
p53	ATC, MTC	44,78
PI3K	ATC, MTC	79,80
mTOR	ATC, MTC	60,81
Histone deacetylase	ATC, MTC	82,83
PDGFR	ATC	51
cABL	ATC	51
Proteasome	ATC, MTC	47
PPARγ	ATC	84
RET	MTC	85
BRAF	ATC	48

ATC = anaplastic thyroid cancer; EGFR = epidermal growth factor-receptor; IGF-IR = insulin-like growth factor-I receptor; MTC = medullary thyroid cancer; mTOR = mammalian target of rapamycin; PDGFR = platelet-derived growth factor-receptor; PI3K = phosphoinositide 3-kinase; PPARγ = peroxisome proliferator-activated receptor gamma; VEGF = vascular endothelial growth factor.

above 45–50 Gy should be administered in order to achieve tumour control.[29] A retrospective analysis of patients treated at MD Anderson revealed no differences in toxicity between intensity modulated radiation therapy (IMRT) and three-dimensional conformal radiation therapy (3DRT).[30]

By increasing the local tumour control rate, distant metastasis become a more important determinant of OS.[8] Consequently, systemic chemotherapy is frequently used to reduce that risk.[31] Doxorubicin either alone or in combination with cisplatin results in usually short-term remissions in 20–30 %. Newer drugs like paclitaxel induce higher remission rates up to 53 %. It is unclear, however, if the use of chemotherapy in this setting translates into prolonged survival.[14,32]

Long-term survival in ATC was only observed in patients who were treated with a combined approach using surgery, radiation and chemotherapy.[7,21,22,24,33] However, the optimal sequence of the available treatment modalities is still a matter of debate.[8] In several studies surgery is used as first line treatment in resectable cases, followed by either radiation or radiochemotherapy.[20,21,26,31,34–36] In more recent studies neoadjuvant radiation or radiochemotherapy preceding surgery and with increased dose from <30 Gy to hyperfractionated doses between 45 and 60 Gy was investigated.[7,37–39] These studies also showed that complete local tumour resection with this multimodality approach is a strong predictor for long term survival. Pre-operative radiation or radiochemotherapy might be advantageous, since it may enhance operability. In addition, surgical biopsy or attempted resection might delay the initiation of further local therapy due to poor wound healing which also favours pre-operative radiation or radiochemotherapy. However, randomised, prospective clinical trials would be necessary to finally clarify the question of the optimal sequence of multimodality treatment.

Molecular Targets in Thyroid Cancer

Targeted agents, focused on inhibition of molecular pathways, are expanding treatment options for patients with a broad spectrum of tumours. Advancing knowledge of the molecular pathogenesis of thyroid cancer and the precise characterisation of potential molecular targets for therapy has led to an increasing number of targeted drugs that are currently being explored in thyroid cancer *in vitro* and *in vivo* (*Figure 2* and *Tables 1–3*). As a result of intense research, several agents have been and currently are investigated in clinical trials and some of them demonstrate significant activity (see *Table 3*). Most of these drugs are tyrosine kinase inhibitors (TKIs) and one of the best explored in MTC, vandetanib, was recently approved by the FDA on the basis of the positive results of a randomised placebo-controlled Phase III trial.[40]

Potential Targets in Medullary Thyroid Cancer

Activating mutations of the RET proto-oncogene are strongly associated with MTC and found in up to 98 % of hereditary and 35–50 % of sporadic forms of MTC, respectively. A variety of mutational hotspots of the RET gene with tumourigenic potential were described.[6] Mutated RET provides mitogenic and survival signals and some specific activating point mutations like M918T appear to be strong negative prognostic indicators for metastasis free survival and OS.[12] Thus it is logical to target RET as a key driving element of MTC.

In familial MTC, loss of heterozygosity in the von Hippel-Lindau (VHL) disease tumour suppressor locus at the somatic level has been described and might be associated with progression of MTC.[41,42] Furthermore, chromosomal imbalance with partial or complete loss of chromosome 3 resulting in a reduced or complete loss of VHL protein expression is reported in MTC.[42] Both events in turn may result in increased expression of the hypoxia-inducible factor I which promotes tumour angiogenesis by overexpression of vascular endothelial growth factor (VEGF). In this context, increased VEGF expression was reported by Capp et al in MTC specimens which provides the rationale for an VEGF-targeted treatment approach.[41] Activation of c-Met triggers tumour growth and angiogenesis and recent data suggest that c-Met is

Table 2: Target Profile of Relevant Molecular Targeted Drugs in Anaplastic Thyroid Cancer and Medullary Thyroid Cancer

Compound	Target	Non DTC histology	Reference
Sorafenib	RET, VEGFR1-3, PDGFR, FLT3, KIT, FGFR, RAF, BRAF	ATC, MTC	66,67,86
Sunitinib	RET, VEGFR2, PDGFR, FLT3, KIT, FGFR	ATC, MTC	87,88
Motesanib	RET, VEGFR1-3, PDGFR, FLT3, KIT	MTC	57
Axitinib	VEGFR1-3, PDGFR, KIT	ATC, MTC	64
Vandetanib	RET, VEGFR2+3, EGFR	MTC	40,89
Gefitinib	EGFR	ATC, MTC	90
Lenvatinib	VEGFR2+3, FGF, SCF	MTC	60
Thalidomide	Angiogenesis	MTC	91
Combretastatin A	Angiogenesis	ATC	62,92
17-AAG	Heat shock protein 90	MTC	93
CS 7017	Peroxisome proliferators-activated receptor-gamma	ATC	10
SAHA	Histone deacetylase	MTC	83
XL184	VEGFR2, MET and RET	MTC	58
PF-03814735	Aurora kinase	ATC	52
Bortezomib	Proteasome	ATC, MTC	47
Everolimus	mTOR	ATC, MTC	81,94,95
Imatinib	BCR-ABL, PDGFR, KIT	ATC, MTC	51,56
Lenvatinib	VEGFR1-3, KIT, PDGFR, FGFR1	MTC	60

ATC = anaplastic thyroid cancer; EGFR = epidermal growth factor-receptor; FGFR = fibroblast growth factor-receptor; MTC = medullary thyroid cancer; mTOR = mammalian target of rapamycin; SCF = stem cell factor; PDGFR = platelet-derived growth factor-receptor; VEGFR1-3 = vascular endothelial growth factor-receptor 1-3.

overexpressed in MTC. Therefore, targeting c-Met might be another attractive therapeutic strategy in MTC.[43] Studies in rodents showed that predisposing factors for the development of MTC are mutations in pRB, p53, PTEN and the cyclin dependent inhibitors p27 and p18 expanding the range of possible targets significantly.[6,44] Further pre-clinical evidence suggest a potential role of the RAS-RAF-ERK, PI3K-AKT, NF-κB pathways as well as protein kinase C and aurora kinases as therapeutic target in MTC.[6,45–47] For additional information see *Table 1*.

Potential Targets in Anaplastic Thyroid Cancer

ATC can either develop *de novo* or through a multistep process from pre-existing differentiated thyroid cancer. This dedifferentiation process is characterised by chromosomal instability and sequential molecular alterations.[1,4] More complex genotypes and specific mutations in genes such as BRAF are often indicative of a more aggressive phenotype 1. It appears that in contrast to MTC, no dominant single genetic change is responsible for tumour growth but rather multiple molecular alterations take place in ATC. Frequently observed mutations involve p53 in up to 80 %, RAS in 70 %, BRAF in 30–60 % and mutations of ß-catenin in up to 70 %.[1,10,48] Other molecular abnormalities in ATC with relevance for molecular targeted therapy are overexpression of the epidermal growth factor-receptor and cyclin E and D in 60–80 and 70 %, respectively.[10,49,50] Compared to normal tissue, thyroid cancer displays a markedly increased vascularisation due to an elevated expression of VEGF. VEGF levels are correlated with tumour local stage and aggressiveness. This makes angiogenesis in thyroid cancer an attractive target for the large battery of vascular targeting agents currently under development or already on the market (*Table 2*).[27] Based on microarray data, it was recently suggested that PDGFR is overexpressed in ATC relative to well differentiated thyroid cancers. Furthermore, it was found to be upregulated in tumours with either mutant or deficient p53. Thus, agents with combined targeting activity against PDGFR and cABL might be promising in ATC.[51]

Overexpression of Aurora kinases was recently demonstrated in ATC cell lines as well as in patient samples, making Aurora kinases inhibition a promising new treatment strategy.[10,52] Recent data from Copland et al. raised the possibility of peroxisomal proliferatior-activated receptor gamma (PPAR-γ as additional target in ATC.[53] A variety of further molecular alterations have been reported in ATC. However, these need to be investigated further or are not amenable to pharmacological targeting. For a comprehensive overview on further molecular alterations in ATC see amongst others the review by Smallridge et al.[10]

Molecular Treatment in Medullary Thyroid Cancer

Multiple clinical trials were conducted or are still ongoing to explore the value of molecular treatment in thyroid cancer. Most of these studies include merely a few patients with MTC and only a limited number of trials focussed on MTC. The majority of clinical trials were conducted with TKIs which have RET and/or the VEGF-system as one of their major targets (see *Table 2*). In several of these Phase II and Phase III studies the therapeutic agents exerted a considerable amount of partial responses and a large proportion of prolonged disease stabilisation (see *Table 3*). Interestingly, activity in MTC was observed not exclusively for agents with designated RET inhibitory activity but also for TKIs without RET inhibitory capacity. This suggests that besides targeting RET other targets like the VEGF system are clinically relevant targets for the treatment of MTC.

In the first large-scale randomised, placebo-controlled Phase III study in MTC, vandetanib met the primary study objective and significantly prolonged the PFS.[40] At present, no final data are available yet since the survival data are still maturing and median PFS is not reached at 24-month follow-up. However, the available data were sufficient for the FDA to grant approval to vandetanib as an orphan drug for the treatment of metastatic or progressive irresectable MTC in April 2011.

Other multi TKIs like sorafenib, axitinib or sunitinib were tested in Phase II trials in thyroid cancer including cases with MTC. Overall, these drugs induced remissions and led to stable disease at a similar rate as vandetanib in[54,55] (see *Table 3*).

In contrast, two studies evaluating the activity of imatinib, an oral TKI of BCR-Abl and KIT, reported no objective response and only a few patients achieved disease stability.[56] Three patients discontinued the

Table 3: Summary of Clinical Data in Anaplastic Thyroid Cancer and Medullary Thyroid Cancer

Compound	Histology	Patients		CR/PR		SD		PD		Reference
		ATC	MTC	ATC	MTC	ATC	MTC	ATC	MTC	
Sorafenib	DTC, ATC, MTC	2	1	0	0	0	1	2	0	67
Sorafenib	ATC	15	-	2	-	4	-	9	-	65
Sorafenib	MTC	-	16	-	1	-	14	-	-	55*
Sorafenib plus tipifarnib	MTC	-	13	-	5	-	4	-	4	61
Axitinib	DTC, ATC, MTC	2	11	1	2	0	3	1	0	64#
Sunitinib	MTC	-	15	-	5	-	4	-	6	54
Imatinib	ATC	11	-	2	-	4	-	2	-	51$
Imatinib	MTC	-	15	-	-	-	4	-	9	56
Fosbretabulin	ATC	18	-	0	-	6	-	12	-	62
Fosbretabulin plus Pac/Carbo	ATC	75	-	NA	-	NA	-	NA	-	92
Vandetanib	MTC	-	30	-	6	-	16	-	8	89
Gefitinib	ATC, MTC	5	4	0	0	1	0	4	4	90
Motesanib	MTC	-	91	-	2	-	74	-	7	57**
XL184	MTC	-	37	-	14	-	15	-		58

**1 patient not evaluable, only patients from Arm B; **8 patients not evaluable; #6 patients indeterminate; $3 patients not evaluable. ATC = anaplastic thyroid cancer; Carbo = carboplatin; CR = complete remission; DTC = differentiated thyroid cancer; MTC = medullary thyroid cancer; NA = not available; Pac = paclitaxel; PD = progressive disease; PR = partial remission; SD = stable disease.*

therapy due to toxicity and dose reductions were required in additional four cases. Schlumberger et al. conducted a trial in MTC patients with the multi TKI motesanib. Although this drug targets both the VEGF-axis and the RET tyrosine kinase, partial tumour responses were observed in only two per cent of patients and disease stabilisation in 48 % lasting more than 24 weeks.[57]

The combined MET, RET and VEGFR2 inhibitor cabozantinib (XL184) exerted meaningful activity in a recent Phase I study including 37 patients with MTC. Twenty-nine per cent confirmed PR and 41 % disease stabilisation lasting for more than six months prompted the launch of the current randomised Phase III study in MTC.[58]

Response data from a recent Phase I trial of lenvatinib (E7080) prompted the launch of a Phase II study in patients with MTC and refractory DTC.[59] Aberrant activation of PIK3/AKT-pathway and mTOR was recently reported in MTC. Based on these data a Phase II study evaluating the activity of everolimus in different types of thyroid cancer including MTC was launched.[60]

From the molecular biology perspective, targeting of different pathways active in thyroid cancer might further increase therapeutic activity. In particular, data from melanoma trials suggested that pathway switching in cancer cells might contribute to resistance to TKI. In order to overcome this phenomenon combined application of drugs targeting different pathways gained attention. In MTC, a first trial was conducted combining sorafenib and the farnesyltransferase inhibitor tipifarnib with a partial remission rate of 38 % and disease stabilisation exceeding six months of 31 %.[61]

Molecular Treatment in Anaplastic Thyroid Cancer

Beside a considerable number of agents in pre-clinical research an increasing number of targeted agents have been explored in ATC. Beyond the most promising class of drugs are TKIs and vascular disrupting agents.

Markedly increased vascularisation and elevated VEGF levels are commonly found in thyroid cancer. VEGF levels appear to correlate with the aggressiveness of the disease providing the rationale for the clinical evaluation of agents directed at vascularisation in ATC. Based on promising results from a Phase I trial, the vascular disrupting agent fosbretabulin was investigated in a Phase II study in 18 patients with ATC as a single agent. There was no objective response but some disease stabilisation (see *Table 3*).[62] Based on reported synergy of fosbretabulin and chemotherapy in pre-clinical studies, a Phase II study assessing the combination of fosbretabulin with a regimen of paclitaxel and carboplatin was initiated. Of the 80 patients included, 75 received therapy. A median survival time of 5.2 months was reported for the combination arm opposed to four months for the standard arm. With a relative reduction in the risk of death by 35 % the one year, survival was 27 % in the combination arm versus 9 % in the standard arm.[63]

In a recent Phase II study by Cohen et al. exploring the activity of the TKI axitinib in thyroid cancer, two patients with ATC were included. Axitinib exerted activity in all histological subtypes including one patient with ATC which experienced a partial remission.[64] In a Phase II study, Nagaiah et al. explored the activity of the broad spectrum TKI sorafenib in 15 patients with ATC.[65] Overall, a disease control rate of approximately 40 % was observed including two partial responses (see *Table 3*). However, time to progression and median OS were not encouraging with 1.9 and 3.5 months respectively. Despite the short PFS and median OS reported, the one year survival was 25 % after treatment initiation.[65] Following initial reports of relatively high response rates of sorafenib observed by Nagaiah, other studies reported more discouraging results.[66,67]

In thyroid cancer, inhibition of tumour-related angiogenesis and BRAF inhibition are of potential therapeutic value and thus it is unclear, whether the observed benefit of the VEGFR1-3 and BRAF-inhibitor sorafenib treatment is related to inhibition of BRAF-kinase or disruption of angiogenesis. In fact, particularly BRAF V600E mutation is associated with higher rate of lymph node metastases and higher TNM stage as well as increased VEGF-expression.[48,60] This would favour a combined VEGF and BRAF inhibitory approach particularly for patients with proven BRAF V600E mutation.

The BCR-ABL and PDGFR inhibitor imatinib is commonly known for its activity in chronic myeloid leukaemia (CML) and gastrointestinal stromal tumour (GIST). Intrigued by the reported overexpression of PDGFR and cABL in ATC, Ha et al. launched a Phase II study of imatinib in ATC. They reported a promising activity with 2/8 evaluable patients showing a PR

and 4/8 achieving stable disease.[51] Further studies to explore the activity of imatinib in ATC seem to be warranted.

PPAR-γ is a member of a superfamily of nuclear hormone receptors, which were recently found to be overexpressed in ATC cell lines. Based on promising activity data from preclinical research a Phase I/II clinical trial was launched to evaluate the activity of the combination of paclitaxel and the oral PPAR-γ agonist CS7017. Preliminary data published by Smallridge et al suggested potential activity of the combination of CS7017 and paclitaxel.[68]

Histone deacetylase inhibitors induce hyperacetylation of histones which results in cellular differentiation, cell cycle arrest and apoptosis. This could result in synergistic interaction between cytotoxic agents like doxorubicin and histone deacetylase inhibitors in ATC.[69]

Conclusion

Despite tremendous research the treatment of advanced and metastatic medullary and anaplastic thyroid cancer hasn't significantly improved until recently.

While there was no active systemic treatment option for metastatic MTC in the past, the introduction of targeted agents clearly improved the prognosis of patients shown in several recent clinical trials, which is highlighted by the FDA approval of vandetanib for the treatment of advanced or metastatic MTC in 2011. Research is continuing and new targeted treatment strategies were recently explored with overall promising results. Particularly to either overcome primary resistance or to override a 'pathway switching', combinations of drugs targeting different key pathways in MTC will potentially further improve the overall cancer related prognosis of MTC patients.

Despite significant progress in decoding the molecular biology of thyroid cancer the outcome of ATC is still dismal. Aggressive multimodal locoregional treatment reduced the rate of local relapse, however due to the lack of active systemic treatment regimens patients die of metastatic disease. New molecular targeted agents are currently in clinical evaluation with partially promising results. Particularly vascular targeting agents like fosbretabulin proved in combination with conventional chemotherapy in one of the largest clinical trials in ATC ever a significant improvement in one-year survival.

With the new therapeutic agents new challenges arise. Based on their therapeutic principle the new agents often affect tumour vitality more rapidly without then inducing significant tumour shrinkage, if at all. Therefore new diagnostic techniques beyond RECIST have to be validated in order to measure activity. These could be more functional measurements like perfusions or changes in tracer accumulation in PET-CT scans.

From the patient perspective, these patients have to be convinced that a long lasting tumour stabilisation is often of higher value than a tumour shrinkage of short duration.

The emerging therapies in thyroid cancer raise new hopes for patients with MTC and ATC. The approval of vandetanib has set the basis to change practice in MTC. Further clinical research is necessary particular in ATC to improve prognosis. Besides approaching new targets like aurora kinases or specific BRAF mutations, targeting the vascular systems definitively warrants further clinical research based on recently published data.

For all involved in thyroid cancer research and treatment it is an inspiring time and it is clear that we indeed are witnessing a new era in the treatment of thyroid cancer. ■

1. Wreesmann VB, Singh B, Clinical impact of molecular analysis on thyroid cancer management. *Surg Oncol Clin N Am,* 2008;17:1–35.
2. Brown LR, Cohen EEW, Novel approaches in the treatment of thyroid cancer, *Update on cancer therapeutics*, 2008;3:1–11.
3. Nagaiah G, Hossain A, Mooney CJ, et al, Anaplastic thyroid cancer: a review of epidemiology, pathogenesis, and treatment, *J Oncol,* 2011:542358.
4. Patel KN, Shaha AR, Poorly differentiated and anaplastic thyroid cancer, *Cancer Control,* 2006;13:119–28.
5. Lebouleux S, Baudin E, Travagli JP, et al., Medullary thyroid carcinoma, *Clin Endocrinol (Oxf),* 2004;61:299–310.
6. Schlumberger M, Carlomagno F, Baudin E, et al., New therapeutic approaches to treat medullary thyroid carcinoma, *Nat Clin Pract Endocrinol Metab,* 2008;4:22–32.
7. Are C, Shaha AR, Anaplastic thyroid carcinoma: biology, pathogenesis, prognostic factors, and treatment approaches, *Ann Surg Oncol,* 2006;13:453–64.
8. Voigt W, Jordan K, Schmoll HJ, Advances in the prognosis and treatment of medullary or anaplastic thyroid cancer, *European Endocrinology,* 2008;4:66–9.
9. Romagnoli S, Moretti S, Voce P, et al., Targeted molecular therapies in thyroid carcinoma, *Arq Bras Endocrinol Metabol,* 2009;53:1061–73.
10. Smallridge RC, Marlow LA, Copland JA, Anaplastic thyroid cancer: molecular pathogenesis and emerging therapies, *Endocr Relat Cancer,* 2009;16:17–44.
11. Rohmer V, Vidal-Trecan G, Bourdelot A, et al., Prognostic factors of disease-free survival after thyroidectomy in 170 young patients with a RET germline mutation: a multicenter study of the Groupe Francais d'Etude des Tumeurs Endocrines, *J Clin Endocrinol Metab,* 2011;96:E509–18.
12. Schilling T, Burck J, Sinn HP, et al., Prognostic value of codon 918 (ATG-->ACG) RET proto-oncogene mutations in sporadic medullary thyroid carcinoma, *Int J Cancer,* 2001;95:62–6.
13. Brandi ML, Gagel RF, Angeli A, et al., Guidelines for diagnosis and therapy of MEN type 1 and type 2, *J Clin Endocrinol Metab,* 2001;86:5658–71.
14. Voigt W, Lorenz K, Schmoll HJ, Therapie des Schilddrüsenkarzinom, *Tumor Diagnostik und Therapie,* 2010;31:18–22.
15. Dralle H, Machens A, Surgical approaches in thyroid cancer and lymph-node metastases, *Best Pract Res Clin Endocrinol Metab,* 2008;22:971–87.
16. Brierley J, Tsang R, Simpson WJ, et al., Medullary thyroid cancer: analyses of survival and prognostic factors and the role of radiation therapy in local control, *Thyroid,* 1996;6:305–10.
17. Fersht N, Vini L, A'Hern R, et al., The role of radiotherapy in the management of elevated calcitonin after surgery for medullary thyroid cancer, *Thyroid,* 2001;11:1161–8.
18. Vitale G, Caraglia M, Ciccarelli A, et al., Current approaches and perspectives in the therapy of medullary thyroid carcinoma, *Cancer,* 2001;91:1797–808.
19. Lorenz K, Brauckhoff M, Behrmann C, et al., Selective arterial chemoembolization for hepatic metastases from medullary thyroid carcinoma, *Surgery,* 2005;138:986–93.
20. Lo CY, Lam KY, Wan KY, Anaplastic carcinoma of the thyroid, *Am J Surg,* 1999;177:337–9.
21. Kihara M, Miyauchi A, Yamauchi A, et al., Prognostic factors of anaplastic thyroid carcinoma, *Surg Today,* 2004;34:394–8.
22. Venkatesh YS, Ordonez NG, Schultz PN, et al., Anaplastic carcinoma of the thyroid. A clinicopathologic study of 121 cases, *Cancer,* 1990;66:321–30.
23. Sugitani I, Kasai N, Fujimoto Y, et al., Prognostic factors and therapeutic strategy for anaplastic carcinoma of the thyroid, *World J Surg,* 2001;25:617–22.
24. Foote RL, Molina JR, Kasperbauer JL, et al., Enhanced survival in locoregionally confined anaplastic thyroid carcinoma: a single-institution experience using aggressive multimodal therapy, *Thyroid,* 2011;21:25–30.
25. Giuffrida D, Gharib H, Anaplastic thyroid carcinoma: current diagnosis and treatment, *Ann Oncol,* 2000;11:1083–9.
26. Haigh PI, Ituarte PH, Wu HS, et al., Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival, *Cancer,* 2001;91:2335–42.
27. Perri F, Lorenzo GD, Scarpati GD, et al., Anaplastic thyroid carcinoma: A comprehensive review of current and future therapeutic options, *World J Clin Oncol,* 2011;2:150–7.
28. Heron DE, Karimpour S, Grigsby PW, Anaplastic thyroid carcinoma: comparison of conventional radiotherapy and hyperfractionation chemoradiotherapy in two groups, *Am J Clin Oncol,* 2002;25:442–6.
29. Pierie JP, Muzikansky A, Gaz RD, et al., The effect of surgery and radiotherapy on outcome of anaplastic thyroid carcinoma, *Ann Surg Oncol,* 2002;9:57–64.
30. Bhatia A, Rao A, Ang KK, et al., Anaplastic thyroid cancer: Clinical outcomes with conformal radiotherapy, *Head Neck,* 2010;32:829–36.
31. De Crevoisier R, Baudin E, Bachelot A, et al., Combined treatment of anaplastic thyroid carcinoma with surgery, chemotherapy, and hyperfractionated accelerated external radiotherapy, *Int J Radiat Oncol Biol Phys,* 2004;60:1137–43.
32. Ain KB, Egorin MJ, DeSimone PA, Treatment of anaplastic thyroid carcinoma with paclitaxel: phase 2 trial using ninety-six-hour infusion. Collaborative Anaplastic Thyroid Cancer Health Intervention Trials (CATCHIT) Group, *Thyroid,* 2000;10:587–94.
33. Veness MJ, Porter GS, Morgan GJ, Anaplastic thyroid carcinoma: dismal outcome despite current treatment approach, *ANZ J Surg,* 2004;74:559–62.
34. Demeter JG, De Jong SA, Lawrence AM, et al., Anaplastic thyroid carcinoma: risk factors and outcome, *Surgery,* 1991;110:956–61.
35. Junor EJ, Paul J, Reed NS, Anaplastic thyroid carcinoma: 91 patients treated by surgery and radiotherapy, *Eur J Surg Oncol,* 1992;18:83–8.
36. Schlumberger M, Parmentier C, Delisle MJ, et al., Combination therapy for anaplastic giant cell thyroid carcinoma, *Cancer,* 1991;67:564–6.
37. Tennvall J, Tallroth E, el Hassan A, et al., Anaplastic thyroid carcinoma. Doxorubicin, hyperfractionated radiotherapy and surgery, *Acta Oncol,* 1990;29:1025–8.
38. Besic N, Auersperg M, Us-Krasovec M, et al., Effect of primary treatment on survival in anaplastic thyroid carcinoma, *Eur J Surg Oncol,* 2001;27:260–4.
39. Kim JH, Leeper RD, Treatment of locally advanced thyroid carcinoma with combination doxorubicin and radiation therapy, *Cancer,* 1987;60:2372–5.
40. Wells Jr SA, Robinson BG, Gagel RF, et al., Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: A randomized, double-blind phase III trial, *J Clin Oncol,* 2012;30:134–41.
41. Capp C, Wajner SM, Siqueira DR, et al., Increased expression of vascular endothelial growth factor and its receptors, VEGFR-1 and VEGFR-2, in medullary thyroid carcinoma, *Thyroid,* 2010;20:863–71.
42. Koch CA, Brouwers FM, Vortmeyer AO, et al., Somatic VHL gene alterations in MEN2-associated medullary thyroid carcinoma, *BMC Cancer,* 2006;6:131.
43. Ivan M, Bond JA, Prat M, et al., Activated ras and ret oncogenes induce over-expression of c-met (hepatocyte growth factor receptor) in human thyroid epithelial cells, *Oncogene,* 1997;14:2417–23.

44. Cerrato A, De Falco V, Santoro M, Molecular genetics of medullary thyroid carcinoma: the quest for novel therapeutic targets, *J Mol Endocrinol,* 2009;43:143–55.
45. Mole D, Gentilin E, Gagliano T, et al., Protein kinase C: A putative new target for the control of human medullary thyroid carcinoma cell proliferation in vitro, *Endocrinology*, 2012;153:2088–98.
46. Baldini E, Arlot-Bonnemains Y, Sorrenti S, et al., Aurora kinases are expressed in medullary thyroid carcinoma (MTC) and their inhibition suppresses in vitro growth and tumorigenicity of the MTC derived cell line TT, *BMC Cancer,* 2011;11:411.
47. Mitsiades CS, McMillin D, Kotoula V, et al., Antitumor effects of the proteasome inhibitor bortezomib in medullary and anaplastic thyroid carcinoma cells in vitro, *J Clin Endocrinol Metab,* 2006;91:4013–21.
48. Caronia LM, Phay JE, Shah MH, Role of BRAF in thyroid oncogenesis, *Clin Cancer Res,* 2011;17:7511–7.
49. Wiseman SM, Masoudi H, Niblock P, et al., Anaplastic thyroid carcinoma: expression profile of targets for therapy offers new insights for disease treatment, *Ann Surg Oncol,* 2007;14:719–29.
50. Elliott DD, Sherman SI, Busaidy NL, et al., Growth factor receptors expression in anaplastic thyroid carcinoma: potential markers for therapeutic stratification, *Hum Pathol,* 2008;39:15–20.
51. Ha HT, Lee JS, Urba S, et al., A phase II study of imatinib in patients with advanced anaplastic thyroid cancer, *Thyroid,* 2010;20:975–80.
52. Wunderlich A, Fischer M, Schlosshauer T, et al., Evaluation of Aurora kinase inhibition as a new therapeutic strategy in anaplastic and poorly differentiated follicular thyroid cancer, *Cancer Sci,* 2011;102:762–8.
53. Copland JA, Marlow LA, Kurakata S, et al., Novel high-affinity PPARgamma agonist alone and in combination with paclitaxel inhibits human anaplastic thyroid carcinoma tumor growth via p21WAF1/CIP1, *Oncogene,* 2006;25:2304–17.
54. Ravaud A, de la Fouchardiere C, Asselineau J, et al., Efficacy of sunitinib in advanced medullary thyroid carcinoma: intermediate results of phase II THYSU, *Oncologist,* 2010;15:212–3.
55. Lam ET, Ringel MD, Kloos RT, et al., Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer, *J Clin Oncol,* 2010;28:2323–30.
56. de Groot JW, Zonnenberg BA, van Ufford-Mannesse PQ, et al., A phase II trial of imatinib therapy for metastatic medullary thyroid carcinoma, *J Clin Endocrinol Metab,* 2007;92:3466–9.
57. Schlumberger MJ, Elisei R, Bastholt L, et al., Phase II study of safety and efficacy of motesanib in patients with progressive or symptomatic, advanced or metastatic medullary thyroid cancer, *J Clin Oncol,* 2009;27:3794–801.
58. Kurzrock R, Cohen EE, Sherman SI, et al., Long-term results in a cohort of medullary thyroid cancer (MTC) patients (pts) in a phase I study of XL184 (BMS 907351), an oral inhibitor of MET, VEGFR2, and RET, *J Clin Oncol,* 2010;28:#5502.
59. Gomez K, Varghese J, Jimenez C, Medullary thyroid carcinoma: molecular signaling pathways and emerging therapies, *J Thyroid Res,* 2011:815826.
60. Kapiteijn E, Schneider TC, Morreau H, et al., New treatment modalities in advanced thyroid cancer, *Ann Oncol,* 2012;23:10–8.
61. Hong DS, Cabanillas ME, Wheler J, et al., Inhibition of the Ras/Raf/MEK/ERK and RET kinase pathways with the combination of the multikinase inhibitor sorafenib and the farnesyltransferase inhibitor tipifarnib in medullary and differentiated thyroid malignancies, *J Clin Endocrinol Metab* 2011;96:997–1005.
62. Cooney MM, Savvides P, Agarwala S, et al., Phase II study of combretastatin A4 phosphate (CA4P) in patients with advanced anaplastic thyroid carcinoma (ATC), *J Clin Oncol,* 2006;24:5580.
63. Sosa RE, Jarzab B, Bal CS, et al., Balkissoon: A randomized phase II/III trial of a tumor vascular disrupting agent fosbretabulin tromethamine (CA4P) with carboplatin (C) and paclitaxel (P) in anaplastic thyroid cancer (ATC): Final survival analysis for the FACT trial, *J Clin Oncol,* 2011;29:abstr 5502.
64. Cohen EE, Rosen LS, Vokes EE, et al., Axitinib is an active treatment for all histologic subtypes of advanced thyroid cancer: results from a phase II study, *J Clin Oncol,* 2008;26:4708–13.
65. Nagaiah G, Wasman JK, Cooney MM, et al., Phase II trial of sorafenib (bay 43-9006) in patients with advanced anaplastic carcinoma of the thyroid (ATC), *J Clin Oncol,* 2009;27:6058.
66. Kloos RT, Ringel MD, Knopp MV, et al., Phase II trial of sorafenib in metastatic thyroid cancer, *J Clin Oncol,* 2009;27:1675–84.
67. Gupta-Abramson V, Troxel AB, Nellore A, et al., Phase II trial of sorafenib in advanced thyroid cancer, *J Clin Oncol,* 2008;26:4714–9.
68. Smallridge R, Copland J, Brose M, Phase 1 study of CS-7017, an oral PPAR-γ agonist, in combination with paclitaxel in advanced anaplastic thyroid cancer. Proceedings of the American Association for Cancer Research 102, 2011.
69. Kim TH, Yoo YH, Kang DY, et al., Efficacy on anaplastic thyroid carcinoma of valproic acid alone or in combination with doxorubicin, a synthetic chenodeoxycholic acid derivative, or lactacystin, *Int J Oncol,* 2009;34:1353–62.
70. Hundahl SA, Fleming ID, Fremgen AM, et al., A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985-1995, *Cancer,* 1998;83:2638–48.
71. Harrington EA, Bebbington D, Moore J, et al., VX-680, a potent and selective small-molecule inhibitor of the Aurora kinases, suppresses tumor growth in vivo, *Nat Med,* 2004;10:262–7.
72. Sorrentino R, Libertini S, Pallante PL, et al., Aurora B overexpression associates with the thyroid carcinoma undifferentiated phenotype and is required for thyroid carcinoma cell proliferation, *J Clin Endocrinol Metab,* 2005;90:928–35.
73. Wang Z, Chakravarty G, Kim S, et al., Growth-inhibitory effects of human anti-insulin-like growth factor-I receptor antibody (A12) in an orthotopic nude mouse model of anaplastic thyroid carcinoma, *Clin Cancer Res,* 2006;12:4755–65.
74. Mitsiades CS, Mitsiades NS, McMullan CJ, et al., Inhibition of the insulin-like growth factor receptor-1 tyrosine kinase activity as a therapeutic strategy for multiple myeloma, other hematologic malignancies, and solid tumors, *Cancer Cell,* 2004;5:221–30.
75. Wynford-Thomas D, Origin and progression of thyroid epithelial tumours: cellular and molecular mechanisms, *Horm Res,* 1997;47:145–57.
76. Kim S, Schiff BA, Yigitbasi OG, et al., Targeted molecular therapy of anaplastic thyroid carcinoma with AEE788, *Mol Cancer Ther,* 2005;4:632–40.
77. Wasenius VM, Hemmer S, Karjalainen-Lindsberg ML, et al., MET receptor tyrosine kinase sequence alterations in differentiated thyroid carcinoma, *Am J Surg Pathol,* 2005;29:544–9.
78. Moretti F, Farsetti A, Soddu S, et al., p53 re-expression inhibits proliferation and restores differentiation of human thyroid anaplastic carcinoma cells, *Oncogene,* 1997;14:729–40.
79. Kunnimalaiyaan M, Ndiaye M, Chen H, Apoptosis-mediated medullary thyroid cancer growth suppression by the PI3K inhibitor LY294002, *Surgery,* 2006;140:1009–14.
80. Saji M, Ringel MD, The PI3K-Akt-mTOR pathway in initiation and progression of thyroid tumors, *Mol Cell Endocrinol,* 2010;321:20–8.
81. Behlendorf T, Voigt W, Mueller T, et al., Activity of mTOR-Inhibitor Rad001 (Everolimus) in differentiated and anaplastic thyroid cancer cell lines, *J Clin Oncol,* 2009;27:14608.
82. Noguchi H, Yamashita H, Murakami T, et al., Successful treatment of anaplastic thyroid carcinoma with a combination of oral valproic acid, chemotherapy, radiation and surgery, *Endocr J,* 2009;56:245–9.
83. Woyach JA, Kloos RT, Ringel MD, et al., Lack of therapeutic effect of the histone deacetylase inhibitor vorinostat in patients with metastatic radioiodine-refractory thyroid carcinoma, *J Clin Endocrinol Metab,* 2009;94:164–70.
84. Weng JR, Chen CY, Pinzone JJ, et al., Beyond peroxisome proliferator-activated receptor gamma signaling: the multi-facets of the antitumor effect of thiazolidinediones, *Endocr Relat Cancer,* 2006;13:401–13.
85. Ball DW, Medullary thyroid cancer: therapeutic targets and molecular markers, *Curr Opin Oncol,* 2007;19:18–23.
86. Capdevila J, Iglesias L, Halperin I, et al., Sorafenib in metastatic thyroid cancer, *Endocr Relat Cancer,* 2012;19;209–16.
87. Cohen EE, Needles BM, Cullen KJ, et al., Phase 2 study of sunitinib in refractory thyroid cancer, *J Clin Oncol,* 2008;26:6025.
88. Ravaud A, de la Fouchardière C, Courbon F, et al., Sunitinib in patients with refractory advanced thyroid cancer: the THYSU phase II trial, *J Clin Oncol,* 2008;26:6058.
89. Wells SA, Jr, Gosnell JE, Gagel RF, et al., Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer, *J Clin Oncol,* 2010;28:767–72.
90. Pennell NA, Daniels GH, Haddad RI, et al., A phase II study of gefitinib in patients with advanced thyroid cancer, *Thyroid,* 2008;18:317–23.
91. Ain KB, Lee C, Williams KD, Phase II trial of thalidomide for therapy of radioiodine-unresponsive and rapidly progressive thyroid carcinomas, *Thyroid,* 2007;17:663–70.
92. Sosa JA, Elisei R, Jarzab B, et al., A randomized phase II/III trial of a tumor vascular disrupting agent fosbretabulin tromethamine (CA4P) with carboplatin (C) and paclitaxel (P) in anaplastic thyroid cancer (ATC): Final survival analysis for the FACT trial, *J Clin Oncol,* 2011;29:5502.
93. Moley JF, Adkins D, Bible KC, et al., 17-allylaminogeldanamycin in advanced medullary and differentiated thyroid carcinoma, *J Clin Oncol*, 2011;29:5582.
94. Faggiano A, Ramundo V, Dicitore A, et al., Everolimus is an active agent in medullary thyroid cancer: a clinical and in vitro study, *J Cell Mol Med,* 2012;16:1563–72.
95. Papewalis C, Wuttke M, Schinner S, et al., Role of the novel mTOR inhibitor RAD001 (everolimus) in anaplastic thyroid cancer, *Horm Metab Res,* 2009;41:752–6.